SUPPLEMENTARY MATERIAL

to

Population-level impact of the BMJ Rapid Recommendation for colorectal cancer screening: a microsimulation analysis

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Appendix 1 – Estimating the distribution of QCancer risk

We used two individual-level data sources to estimate the distribution of QCancer risk in the Swiss population. For the main analysis, we used the population-based Swiss Health Survey (SHS). For our fifth sensitivity analysis, we used the outcomes of the overarching trial of this modelling study: the PREcision ScreENing randomized controlled Trial (PRESENT).

1.1 – Swiss Health Survey

For our main analysis, we used the written questionnaire of the Swiss Health Survey (SHS) 2012. Compared to SHS 2017, it includes more questions on prior cancer diagnoses which are needed to compute QCancer risk.[4] Table S1.1 describes for each risk factor used in the QCancer calculator[5] its applicability in the Swiss situation. If it applied, the table indicates which SHS variables were used to derive the required values, along with additional remarks.

The written questionnaire of SHS 2012 had 14,414 respondents that were old enough to apply QCancer (≥25 years old) and not too old for screening (<75 years). Table S1.2 shows their baseline characteristics. Since all individuals in SHS were weighted, the table shows the characteristics in terms of these weights.

1.1.1 – Imputation of previous cancer diagnoses

QCancer requires to inform if someone has been previously diagnosed with certain cancer types. SHS only records if individuals have been diagnosed with a cancer in the past year (variable SKRAN25a) or have ever been treated for a cancer (variable SKRAN25b). We assumed that all cancer diagnoses made more than a year ago had also been treated. This allowed us to combine these two variables to determine if someone ever had a cancer.

Next, for each person that ever had a cancer according to the combined variable, we imputed a cancer type. We used the age- and sex-specific 10-year prevalence of cancer types in 2012 in Switzerland to determine the proportion of the population which is assigned a certain cancer type.[2] Figure S1.1 shows with narrow lines the age-specific 1, 2, 5 and 10-year prevalence of all cancers in Switzerland combined for males and females. In bold, it shows the responses to the SHS on the questions “Have you been diagnosed with cancer in the past 12 months?”, “Have you been treated for cancer in the past 12 months?” and “Have you ever been treated for cancer?”. It also shows in bold blue the variable that combines “Have you ever been treated for cancer?” and “Have you been diagnosed with cancer in the past 12 months?”, which we used for the imputations. The 10-year cancer prevalence most closely approaches our combined variable, and was therefore used for the imputations.

Table S1.1 – Overview of the risk factors used in the QCancer calculator and their relation to SHS. Some questions were not used, and some had to be imputed.

	Risk factor in QCancer calculator	Applied	Corresponding SHS variables	Remarks
1	Age	Yes	ALTER	
2	Sex	Yes	SEX	
3	Ethnicity	No		Not recorded in SHS, so all SHS respondents are assumed "White or not stated".
4	Postcode	No		Postcode deprivation score not available in SHS.
5	Smoking status	Yes	TABAC3 and NICOT5	
6	Alcohol status	Yes	AGRAMTAG and TALKO15	We assumed 1 unit of alcohol equaled 8 grams of alcohol.
7	Do you have a family history of gastro-intestinal cancer?	Yes	None	Imputed based on Sandhu et al.[1]
8	Have you had any of these cancers? Females: Breast, Uterine, Ovarian, Cervical Males: Oral, Lung, Blood	Yes	SKRAN25a and SKRAN25b	We assumed that all individuals diagnosed with cancer over a year ago had also been treated. The cancer type was imputed with cancer prevalence data from the Swiss registry[2].
9	Do you currently have diabetes type 2?	Yes	TDIAB01	We assumed that all SHS responders with diabetes had diabetes type 2.
10	Do you currently have ulcerative colitis?	No		Exclusion criterion for CRC screening.[3] We assumed that all individuals in our simulations responded "No".
11	Do you currently have colonic polyps?	No		Exclusion criterion for CRC screening.[3] We assumed that all individuals in our simulations responded "No".
12	BMI (males only)	Yes	TGEZU01 and TGEZU02	BMIs <18 and >47 were set to 18 and 47, respectively.

Table S1.2 – Baseline characteristics of the individuals included in the SHS and PRESENT data. For SHS, percentages are based on SHS weights. For PRESENT, percentages are based on the number of individuals because individuals were not weighted. BMI = Body Mass Index; NA = Not Applicable; SHS = Swiss Health Survey; PRESENT = PREcision ScreENing randomized controlled Trial

	Swiss Health Survey										**PRESENT**
Age group	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**50-74**
Number of individuals	971	1202	1364	1715	2004	1756	1452	1416	1472	1062	806
Total SHS weight	515436	555137	516270	634275	746148	558862	518337	452026	453389	317762	NA
Sex											
Female	48.0%	50.7%	47.5%	52.7%	49.0%	49.3%	48.4%	51.4%	50.7%	54.4%	51.9%
Male	52.0%	49.3%	52.5%	47.3%	51.0%	50.7%	51.6%	48.6%	49.3%	45.6%	48.1%
Smoking status											
Non-smoker	49.0%	44.8%	47.7%	50.5%	49.3%	43.5%	39.9%	45.5%	43.2%	52.3%	53.8%
Ex-smoker	13.7%	18.3%	16.8%	20.2%	21.1%	28.2%	30.4%	28.8%	36.0%	33.7%	32.9%
Light	18.3%	20.3%	16.8%	12.3%	13.3%	10.6%	11.8%	11.0%	8.6%	6.7%	7.8%
Moderate	12.2%	10.4%	11.2%	8.6%	8.7%	8.3%	8.2%	7.3%	7.2%	4.1%	3.6%
Heavy	6.9%	6.0%	7.6%	8.3%	7.4%	9.4%	9.8%	7.3%	4.9%	2.9%	1.6%
Unknown	0.0%	0.2%	0.1%	0.1%	0.0%	0.0%	0.0%	0.1%	0.0%	0.4%	0.2%
Alcohol status (units per day)											
None	26.8%	27.9%	24.6%	26.6%	23.5%	21.1%	22.5%	24.4%	23.4%	28.3%	11.2%
<1 unit	41.6%	43.3%	45.8%	43.3%	44.0%	44.2%	40.7%	37.2%	33.8%	33.0%	17.9%
1-2 units	24.7%	21.4%	24.0%	23.5%	25.0%	26.7%	25.1%	27.1%	29.5%	27.1%	43.7%
3-6 units	5.5%	6.5%	4.7%	5.0%	5.8%	6.9%	11.1%	9.5%	11.4%	10.5%	23.2%
7-9 units	1.5%	0.6%	0.6%	1.0%	1.3%	0.6%	0.4%	1.0%	1.2%	0.9%	1.5%
9+ units	0.0%	0.3%	0.3%	0.5%	0.3%	0.5%	0.2%	0.8%	0.6%	0.2%	0.9%
Unknown	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.0%	1.7%
Has diabetes	1.0%	0.7%	1.4%	1.6%	3.5%	3.2%	5.6%	7.6%	10.9%	11.9%	2.5%
Unknown	0.0%	0.0%	0.1%	0.0%	0.1%	0.2%	0.3%	0.1%	0.1%	0.0%	1.1%
Mean BMI (males only)	23.5	23.8	24.1	24.6	24.9	25.2	25.5	26.0	26.1	25.9	26.4
Unknown	0.3%	0.3%	1.4%	0.5%	0.3%	0.4%	0.4%	1.3%	0.3%	0.7%	0.5%
Had a prior cancer diagnosis*	1.7%	1.2%	2.4%	3.9%	3.7%	4.5%	6.2%	8.4%	9.9%	9.9%	3.0%
Unknown	0.3%	1.2%	1.0%	0.9%	1.4%	1.5%	2.6%	2.5%	2.6%	3.9%	0.0%

**For SHS, this includes positive responses to at least one of the questions "Have you ever been treated for cancer?" and "Have you been diagnosed with cancer in the past year?". This includes all types of cancer. For PRESENT, this includes positive responses to the question "Have you ever been diagnosed with cancer?" and only includes the cancer types that are relevant for QCancer (breast, cervix, ovary, uterine for females; oral, lung, blood for males)*

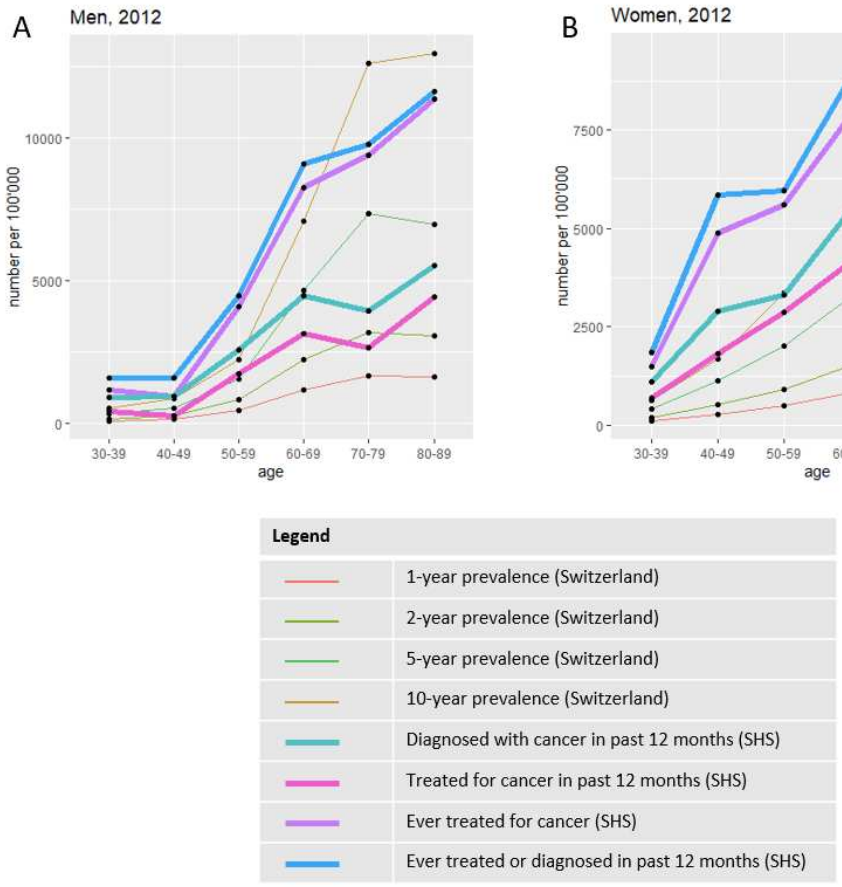

Figure S1.1 – Comparison of the prevalence of cancer as reported in Switzerland (NACR) in 2012 and the relevant variables in SHS 2012 for A) males and B) females.

1.1.2 – Imputations of family history of GI cancers

SHS does not report family history of GI cancers. It neither has a suitable proxy. We therefore randomly assigned a family history to individuals, according to the sex- and age-specific prevalence of family history of CRC as reported for the UK by Sandhu et al.[1]

In our third sensitivity analysis, we assumed a higher proportion of the population had a family history of GI cancer (on average 10% instead of 7.3%). This was done because we used the prevalence of *CRC* family history for our imputations, while the QCancer tool uses the family history of *GI* cancers which is likely to be higher.

In our fourth sensitivity analysis, we assumed that a lower proportion of the population had a family history of CRC (on average 4.87%). This was done because we used the estimated prevalence of CRC family history from the UK for our imputations, while CRC incidence in the UK is approximately 50% higher than in Switzerland.[6] Therefore the prevalence of family history of CRC is likely to be lower in Switzerland compared to the UK.

The family histories that we used in the base case and the third and fourth sensitivity analyses are displayed in Table S1.3. We used the family history prevalence of the age group 40-49 to impute the family history for individuals aged 25 to 39.

Table S1.3 – Used prevalence of family history of GI cancers in the base case and the two sensitivity analyses with increased (multiplied by 1.4 such that the overall prevalence is 10%) and decreased family history (multiplied by 1/1.5).

	Base case [1]			Sensitivity analysis 3 – Increased prevalence of GI cancer family history			Sensitivity analysis 4 – Decreased prevalence of GI cancer family history		
Age	Women	Men	Total	Women	Men	Total	Women	Men	Total
40-49	6.0%	4.4%	5.3%	8.4%	6.2%	7.5%	4.0%	2.9%	3.6%
50-59	7.6%	6.9%	7.3%	10.7%	9.6%	10.2%	5.1%	4.6%	4.9%
60-69	9.1%	6.8%	8.0%	12.8%	9.5%	11.2%	6.1%	4.5%	5.3%
70-75	9.7%	7.8%	8.8%	13.6%	10.9%	12.3%	6.5%	5.2%	5.9%
Total	8.0%	6.5%	7.3%	11.2%	9.1%	10.2%	5.3%	4.3%	4.9%

1.1.3 – Heterogeneity due to the imputations

Besides prior cancer diagnoses and family history, we also imputed the missing values of all other SHS variables. We used the Multiple Imputation with Chained Equations (MICE) algorithm[7] in R to generate 50 datasets by doing 50 imputations of all variables (prior cancer diagnoses, family history and unknown values). For each dataset, we used five iterations in the MICE algorithm. Using the generated datasets, we calculated the QCancer-predicted risk for each individual and generated the distribution of QCancer risk. This way, we evaluated if the imputations resulted in heterogeneity of the risk distribution.

To assess the heterogeneity of imputations in the SHS data, we plotted in Figure S1.2 the empirical cumulative distribution functions of the 50 imputed QCancer risk distributions, each in a separate colour. We presented both the risks between 0% and 10% (left panel) and the risks between 0% and 4% (right panel) as this latter risk range is most relevant to our analyses. We observed that the risk distribution is very stable, also for QCancer risks between 0% and 4%.

Since the heterogeneity between the imputed risk distributions is very limited, we chose the median of these 50 distributions for the remainder of our analysis.

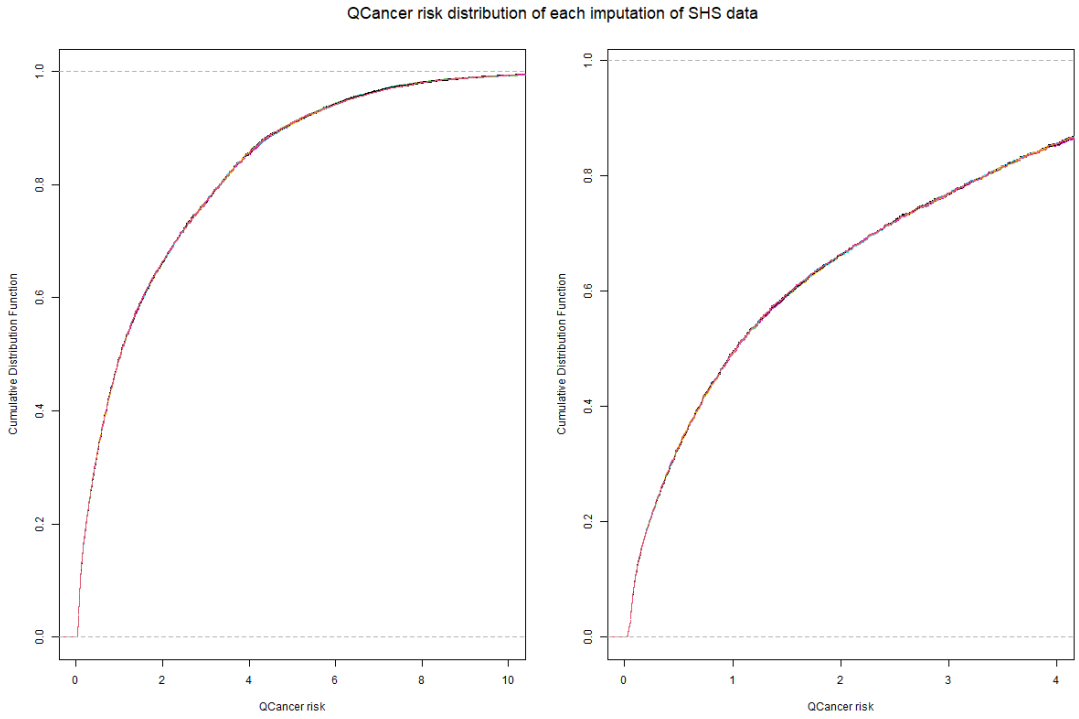

Figure S1.2 – The empirical cumulative distribution functions of the absolute QCancer risk obtained from SHS for QCancer risks 0%-10% (left panel) and 0%-4% (right panel). Each coloured line represents one of the 50 imputations.

1.2 – PRESENT study

The organized CRC screening program in the canton of Vaud invites individuals aged 50 to 69. They are offered a choice between biennial Fecal Immunochemical Test (FIT) screening or 10-yearly colonoscopy screening.[3] Ideally, individuals at high risk of CRC choose colonoscopy and those at low risk choose FIT after discussion with their GP. However, this is not always the case in practice. The PRESENT study is a pilot randomized controlled trial to investigate the effect of personalized recommendations for FIT or colonoscopy screening appropriate to an individual's QCancer-predicted risk.[8]

In our fifth sensitivity analysis, we used the QCancer risk scores of the participants in the trial to estimate the distribution of QCancer-predicted risk in this population. Advantageously, the questionnaire included all relevant questions for the QCancer calculator, resulting in fewer missing data. However, the number of responders was limited (n=901) of which 95 participants were excluded because they reported 1) a genetic risk for CRC or inflammatory bowel disease, 2) being under regular surveillance for polyps, or 3) having had CRC before. The characteristics of the remaining 806 individuals are shown in the last column of Table S1.2. As the trial recruited individuals that had not been screened before, over 90% of the responders was aged 50 to 53. To obtain the risk distributions of the separate age groups, the prevalence of the risk factors was assumed independent of age (see Appendix 3.4).

1.2.1 – Heterogeneity due to imputations

Although all risk factors in the QCancer calculator were included in the questionnaire, the PRESENT study data still had some missing responses (see Table 1 in manuscript). As with the SHS data, missing values were imputed 50 times with the MICE algorithm to evaluate the heterogeneity due to the imputations. The empirical cumulative distribution functions of the 50 imputed QCancer risk distributions for the PRESENT data are shown in Figure S1.3. Similarly, the risk distribution generated by the PRESENT data is stable with respect to the imputations.

We observe that the predicted risk distributions from SHS cover a wider range of QCancer risks compared to the distributions obtained from the PRESENT study. This is likely explained by the narrower age range of the participants in the PRESENT study (See Appendix 3.4).

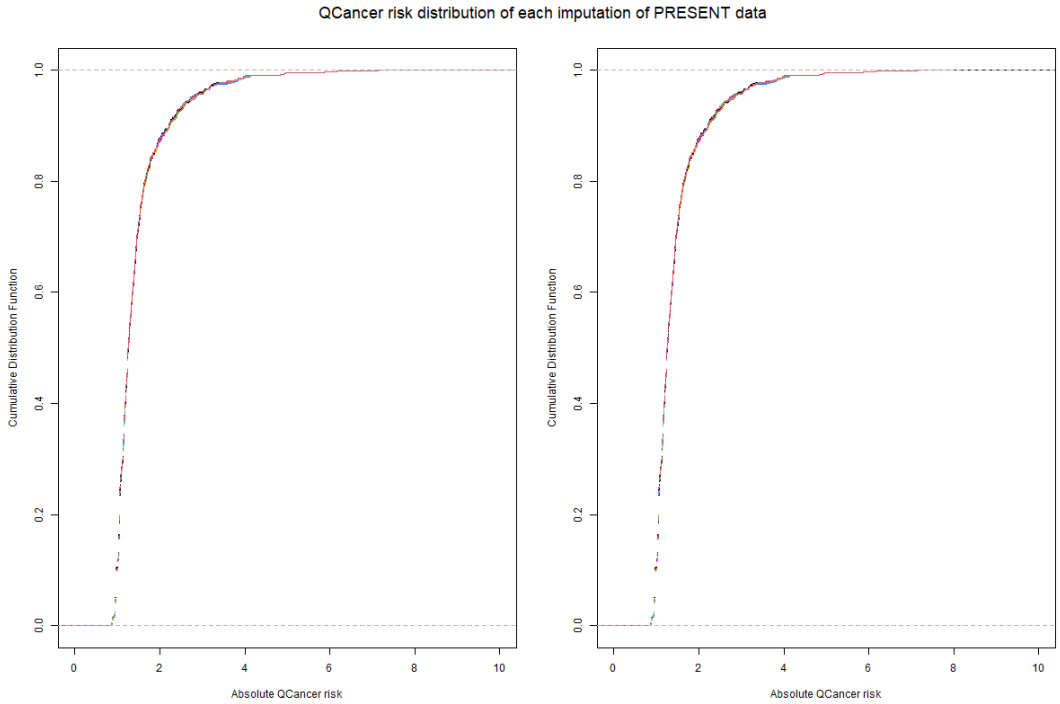

Figure S1.3 – The empirical cumulative distribution functions of the QCancer risk obtained from PRESENT for QCancer risks 0%-10% (left panel) and 0%-4% (right panel). Each coloured line represents one of the 50 imputations.

Appendix 2 – Calibration of MISCAN-Colon

MISCAN-Colon is a stochastic microsimulation model. The model has been described extensively in previous publications.[9,10] To develop a reliable version of MISCAN-Colon for our study, we adapted and recalibrated the model to Switzerland, similar to the approach by Gini et al.[11]

2.1 – Calibration procedure

We started using the previously calibrated model for The Netherlands and adjusted specific demographics and CRC epidemiological assumptions to create sex-specific models for Switzerland:

- We used the all-cause mortality tables from 2019 (before COVID) from the Federal Statistical Office of Switzerland;
- We incorporated the CRC subsite distribution using data from 1985-1989, before (opportunistic) CRC screening occurred, obtained from the National Agency for Cancer Registration (NACR). It included data from six registries covering nine out of the 26 Swiss cantons: both Appenzell (AR, AI), Basel City and Land (BS, BL), Geneva (GE), Neuchâtel (NE), Sankt-Gallen (SG), Vaud (VD), and Zurich (ZH).
- We adjusted the input parameters for CRC survival by comparing the subsite (colon and rectum) and stage-specific 5-year relative survival observed in The Netherlands and Switzerland in the period 2014-2018. The ratio between the two survival rates was subsequently used as a multiplicative factor to adjust the MISCAN-Colon age-, stage- and subsite-specific CRC relative survival model parameters from the Dutch MISCAN-Colon model. The Swiss survival rates were obtained from NACR and included all Swiss cantons except Aargau (AG), Freiburg (FR), Schaffhausen (SH) and Schwyz (SZ).

Next, we calibrated two sets of model parameters. First, we assumed a similar biology (cancer pathway) for CRC development in The Netherlands and Switzerland. This implied that the difference in CRC incidence between the two countries is explained by a difference in risk of adenoma onset. We calibrated the parameters for age-specific risk of adenoma onset such that the model aligned with the Swiss CRC incidence. Second, we assumed that the difference in CRC stage distribution between The Netherlands and Switzerland was caused by differences in access to care, in absence of screening, between the two countries. We therefore recalibrated the probabilities of CRC diagnosis in each stage to the Swiss CRC stage distribution. A genetic algorithm was used for calibration.[12]

- We used the Swiss CRC incidence from the period 1985-1989 as calibration targets, obtained from NACR for the nine Swiss cantons mentioned earlier.
- We also used the Swiss CRC stage distribution by subsite (left colon, right colon and rectum) from the period 1985-1989 as calibration target. We only used data from the registry of the canton of Geneva, because it was the only one with sufficiently complete data.

Finally, we validated the model by comparing the model-predicted CRC mortality with the observed CRC mortality in Switzerland.

- We used the total Swiss CRC mortality from the periods 1985-1989, 1995-1999 and 2010-2014 as validation targets. Data were obtained from NACR and included the whole of Switzerland.
- We adjusted the model parameters for CRC survival to the time periods 1985-1989 and 1995-1999. As described before, we compared the subsite-specific CRC survival (colon and rectum) from Switzerland from these periods[13,14] with the Swiss CRC survival from the period 2010-2014.

2.2 – Calibration results

Figures S2.1 and S2.2 show the calibration results for the age-specific CRC incidence of the models for females and males, respectively. The black dots with confidence intervals are the observed Swiss data, the red line represents the model output. Although slightly underestimating the incidence for the 80-84 and 85+ age groups, the model-predicted incidence fits the pattern of the observed incidence well.

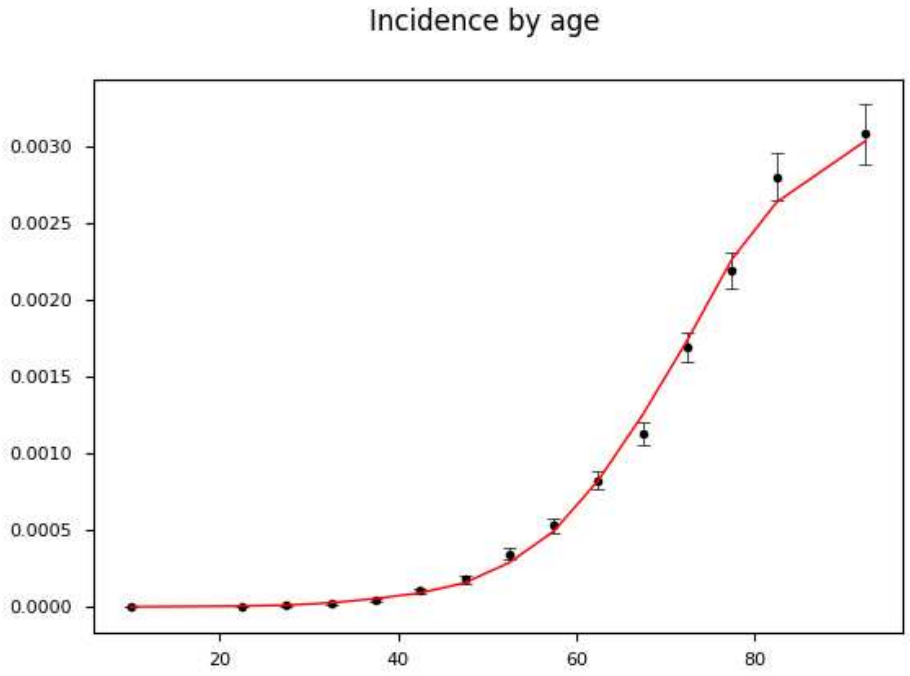

Figure S2.1 – The model-predicted and observed age-specific CRC incidence rates per 100,000 females in Switzerland.

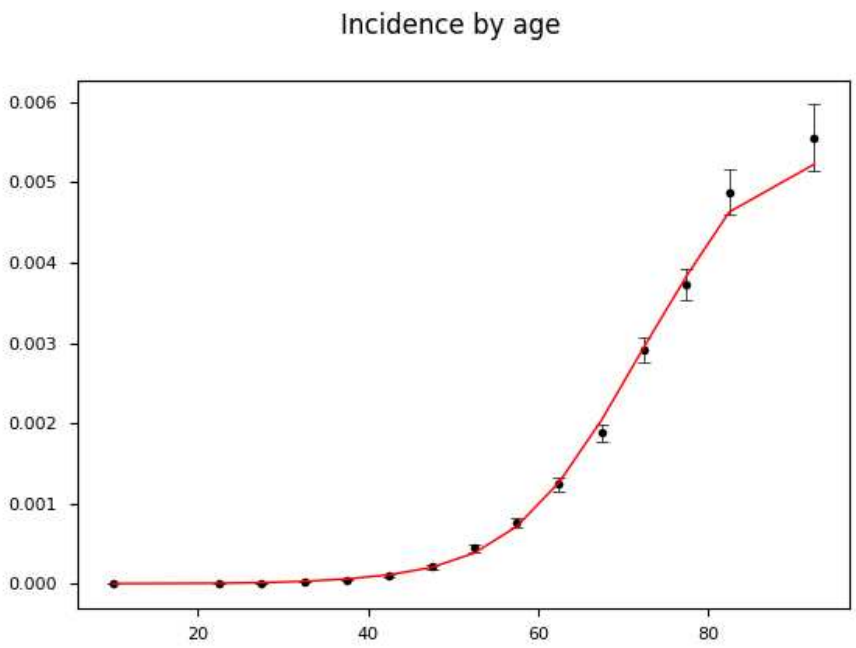

Figure S2.2 – The model-predicted and observed age-specific CRC incidence rates per 100,000 males in Switzerland.

2.3 – Validation results

Figure S2.3 shows the overall mortality rate as predicted by MISCAN and observed in the Swiss population. Remarkably, the model highly underestimates the CRC mortality in 1985-1989. However, until 1995, CRC mortality in Switzerland included all individuals that died **with** CRC whereas we modelled individuals that died **of** CRC.[15] The Swiss coding protocol was changed in 1995, and we observe that our model is able to replicate mortality in the period 1995-1999, slightly overestimating mortality rates between ages 70-84. Compared to 1995-1999, the model overestimates CRC mortality more in 2010-2014. This is possibly due to (opportunistic) CRC screening introduction in Switzerland by that time, and we did not incorporate screening in MISCAN for this validation procedure.

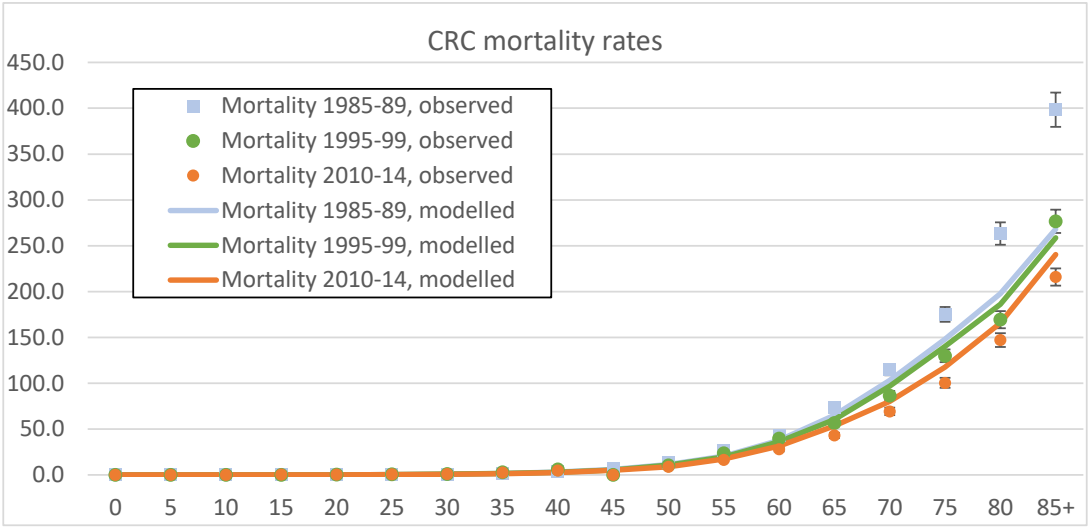

Figure S2.3 – Model-predicted and observed age-specific CRC mortality rates per 100,000 persons in Switzerland for the 5-year periods 1985-1989, 1995-1999 and 2010-2014.

Appendix 3 – Risk prediction in MISCAN-Colon

After obtaining the distribution of QCancer risk as described in Appendix 1, we incorporated it in MISCAN to simulate risk prediction using an elliptical copula. This approach has been applied before in modelling studies of risk-based screening based on polygenic risk scores.[16,17] However, the polygenic risk scores in these studies were independent of age, whereas QCancer risk scores are age-dependent. We therefore adjusted the methodology to incorporate the age dependency of QCancer. We describe the methodology in 3 steps. Although only SHS is mentioned in these steps, the same approach was used for the fifth sensitivity analysis which used the PRESENT data.

In short, individuals with a higher underlying risk of developing adenomas in MISCAN-Colon are more likely to get assigned a higher QCancer-predicted risk. This assumes that their increased underlying risk is caused by, for example, more intensive smoking behaviour or a family history of GI cancer. However, not all CRC cases are attributable to the risk factors included in the QCancer tool only. Thus, underlying and QCancer-predicted risk are not perfectly correlated. We calibrated this correlation using an elliptical copula approach.

3.1 – QCancer-risk distribution for each feasible screening start age

The written questionnaire of the SHS 2012 included 14,414 respondents of whom, for example, 164 were 50-year-old males. This would be too few to derive the QCancer risk distribution for each sex and age separately (e.g. determine the QCancer risk distribution for males aged 50), also because the SHS weights do not adjust for risk factors in QCancer such as BMI, cancer diagnoses and diabetes. We therefore generated 10 quinquennial age groups of SHS respondents (ages 25-29, 30-34, …, 65-69, 70-74) for which we derived the QCancer risk distribution. Figure 1 in the main text shows the sex-specific risk distribution of the total population and the different age groups.

In our simulations, we assumed that all individuals completed the QCancer questionnaire every five years, starting at age 25 and ending at age 70, to determine their screen-eligibility. As such, we needed the QCancer risk distribution for these specific ages only. We adjusted the age of all individuals in a quinquennial age group to the corresponding start age (e.g. the age of all respondents in SHS aged 50-54 was adjusted to 50). Next, we calculated the risk score of all individuals with these adjusted ages to derive the QCancer risk distribution specifically for the screening start ages. This approach assumes that the distribution of all risk factors except age does not change within a quinquennial age group. For example, the prevalence of individuals with diabetes at age 54 is the same as for those aged 50.

As such, we derived 20 QCancer risk distributions: one for each screening start age (25, 30, …, 70) and sex. Figure S3.1 shows the resulting QCancer risk distribution of the total population and the different age groups. After that, we smoothened all separate QCancer risk distributions with Kernel Density estimation, using the “density” function in R.

To determine the distribution of the age to start screening for a specific risk threshold, we calculated the fraction of individuals that exceeded the risk threshold at all possible screening start ages, and subtracted the fractions of two consecutive ages. So, for each screening start age, we represented the proportion of “new” individuals that exceeded the threshold in Figure 2 in the main text.

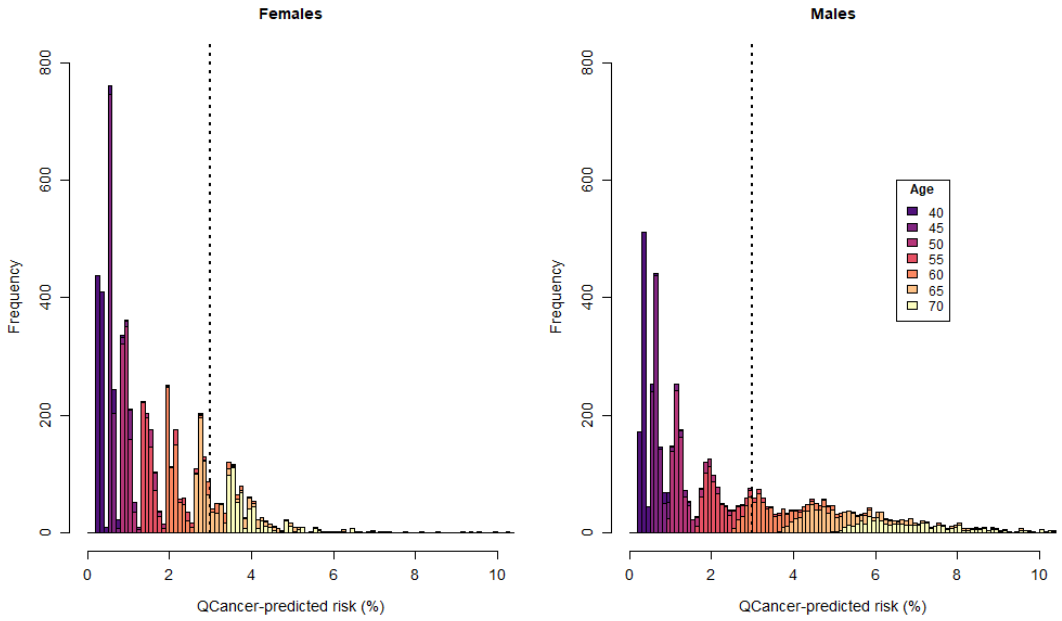

Figure S3.1 – Distribution of QCancer-predicted risk in the full Swiss Health Survey cohort stratified by sex, after rounding down the age to a multiple of 5. The colors represent the distributions of the (combined) 5-year age groups. The vertical, dotted line indicates the 3% risk threshold for screening as recommended by the BMJ Rapid Recommendation.

3.2 - Copula linking underlying risk and QCancer risk

In MISCAN-Colon, each simulated individual is assigned an *underlying* "true" risk of developing adenomas. The distribution of this underlying risk in the population was previously calibrated to match international adenoma prevalence and CRC incidence estimates.[10] In reality, the underlying risk remains unobservable: we can only observe the predicted risk as determined by QCancer. Therefore, during the simulation, every individual was also assigned a QCancer-*predicted* risk whenever they completed the QCancer tool. This predicted risk was based on their sex, current age, underlying risk and QCancer's predictive accuracy.

An individual's predicted and underlying risk typically do not align perfectly due to the predictive limitations of QCancer. Nevertheless, there is a correlation ρ between the predicted and underlying risk, and the strength of this correlation depends on the accuracy of QCancer. We calibrated this correlation using an elliptical copula approach.[18] The underlying assumption to that approach is that the discriminatory power of QCancer is represented by the spread of relative risk scores in the population. For example, if QCancer assigns a wide range of relative risk scores, it might distinguish well between individuals of different risk levels, whereas this will not be the case if it assigned a narrow range of risk scores.

The risk indices in MISCAN-Colon were used as starting point. In MISCAN-Colon, the distribution of underlying risk is assumed to be a Gamma distribution with mean 1 and variance 2.66755.[10] We split the simulated population in 60 different underlying relative risk (URR) groups with URR ranging from 0.1 to >6 with increments of 0.1. Then, we transformed each age- and sex-specific QCancer risk distribution to a relative risk distribution by dividing by their means. We also split these distributions in 60 different predicted relative risk (PRR) groups with PRR ranging from 0.1 to >6 with increments

of 0.1. Next, for each PRR group, we determined the distribution of URR groups. For example, in the PRR group with PRR>6 we expect that most individuals will be in a high URR group. In turn, most individuals with PRR=0.1 should be in a low URR group. However, QCancer is likely to misclassify the risk of individuals, so individuals with a high URR can have a low PRR, and vice versa.

In our study, the copula is a joint probability distribution that links two marginal distributions: the underlying risk distribution in MISCAN and one of the age- and sex-specific QCancer risk distribution. We calibrated the correlation parameter ρ of the copula for each age and sex group to obtain 20 joint distribution of underlying and predicted risk (Figure S3.2). From this we could find, for each PRR group, the fraction of individuals with a certain URR, given the age and sex. During calibration, we respected the following three criteria:

1. The average URR of a PRR group equals the PRR of that group. In other words, of all individuals with a PRR of 1.3, the average URR will also be 1.3 (Figure S3.3).
2. The discriminatory accuracy of QCancer is maintained for each age- and sex-group. That is, the distribution of QCancer risk in the joint distribution is the same as the risk distribution derived from SHS for a certain age and sex. (Figure S3.4).
3. For all age and sex-groups, the underlying risk distribution in MISCAN-Colon is maintained. That is, the distribution of underlying risk in all PRR groups sums to the Gamma distribution with mean 1 and variance 2.66755 (Figure S3.5).

In general, the obtained correlations were very low, not exceeding 0.3. This aligns with Figure S3.2 which shows that the correlation between the two risk indices is very small.

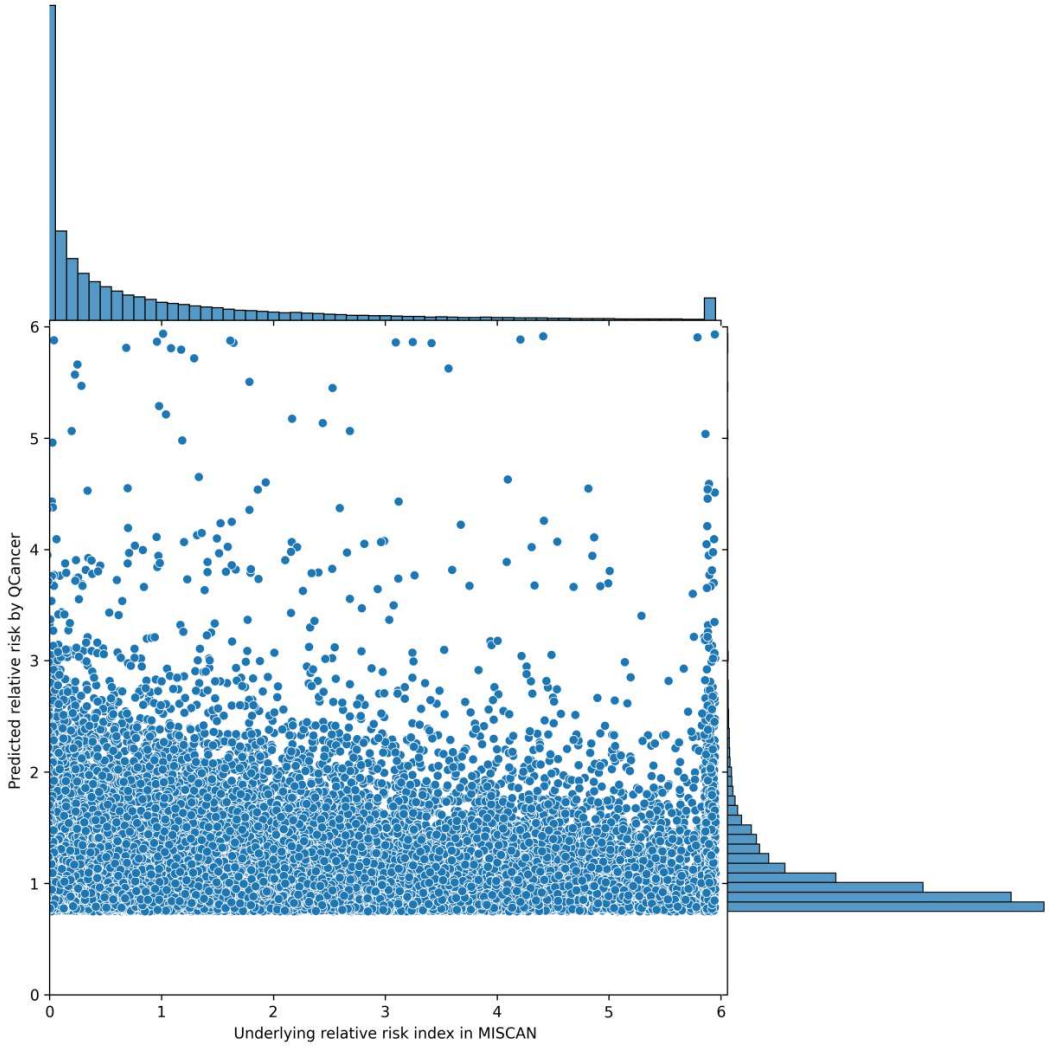

Figure S3.2 – Joint distribution (calibrated elliptical copula) of underlying and predicted relative risks for 50-year-old males (bottom left). The top distribution is the marginal distribution of underlying risk in MISCAN. The distribution on the right is the QCancer risk distribution for 50-year-old males. The copula combines both marginal distributions into a joint distribution.

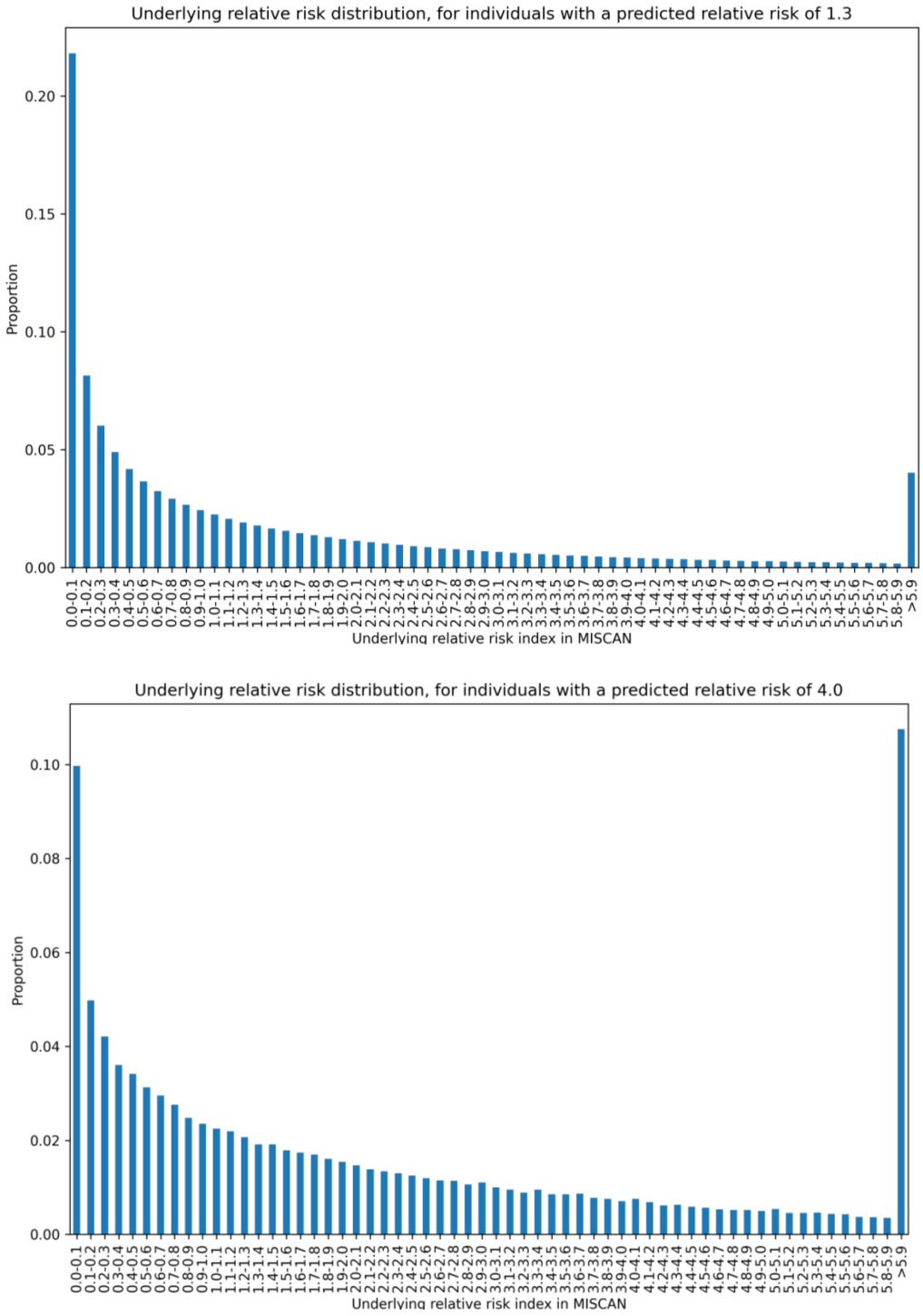

Figure S3.3 – Distribution of underlying relative risk in the MISCAN-Colon model for all individuals with a predicted relative risk of 1.3 (top) and 4.0 (bottom). The average underlying relative risk of these individuals also equals 1.3 and 4.0, respectively. These figures are horizontal intersections in Figure S3.2.

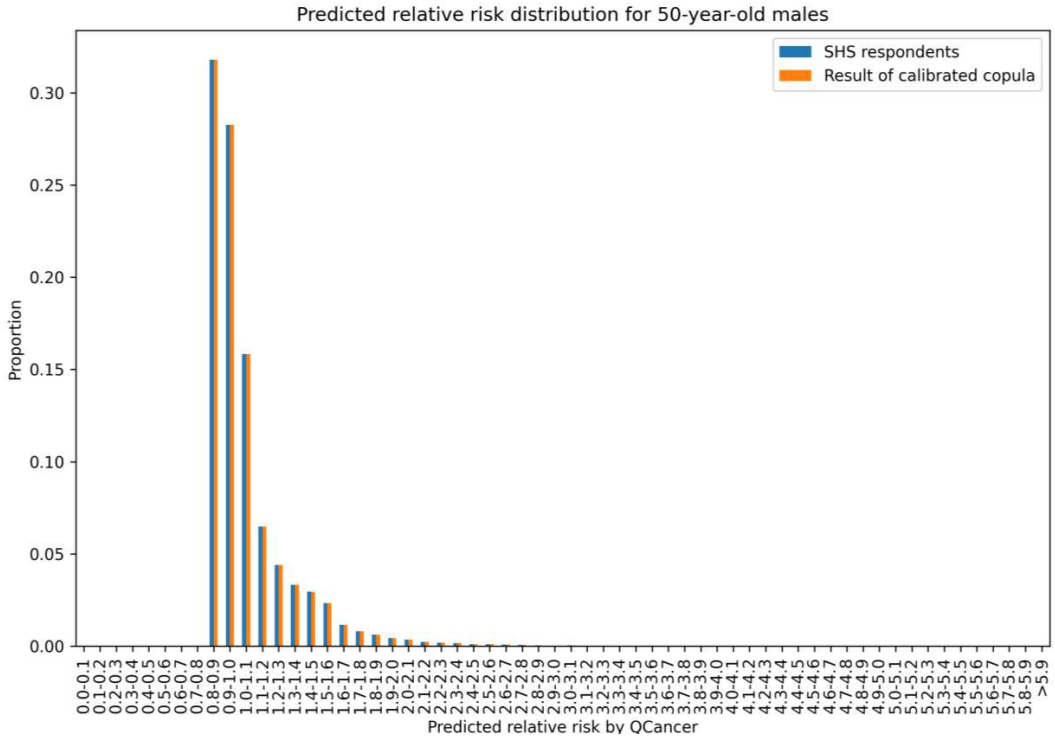

Figure S3.4 – Original distribution of predicted relative risk by QCancer in 50-year-old males (SHS respondents, blue), and the marginal distribution obtained with the copula (orange). The orange is the marginal distribution on the right in Figure S3.2. The two are nearly equal which is in line with criterion 2.

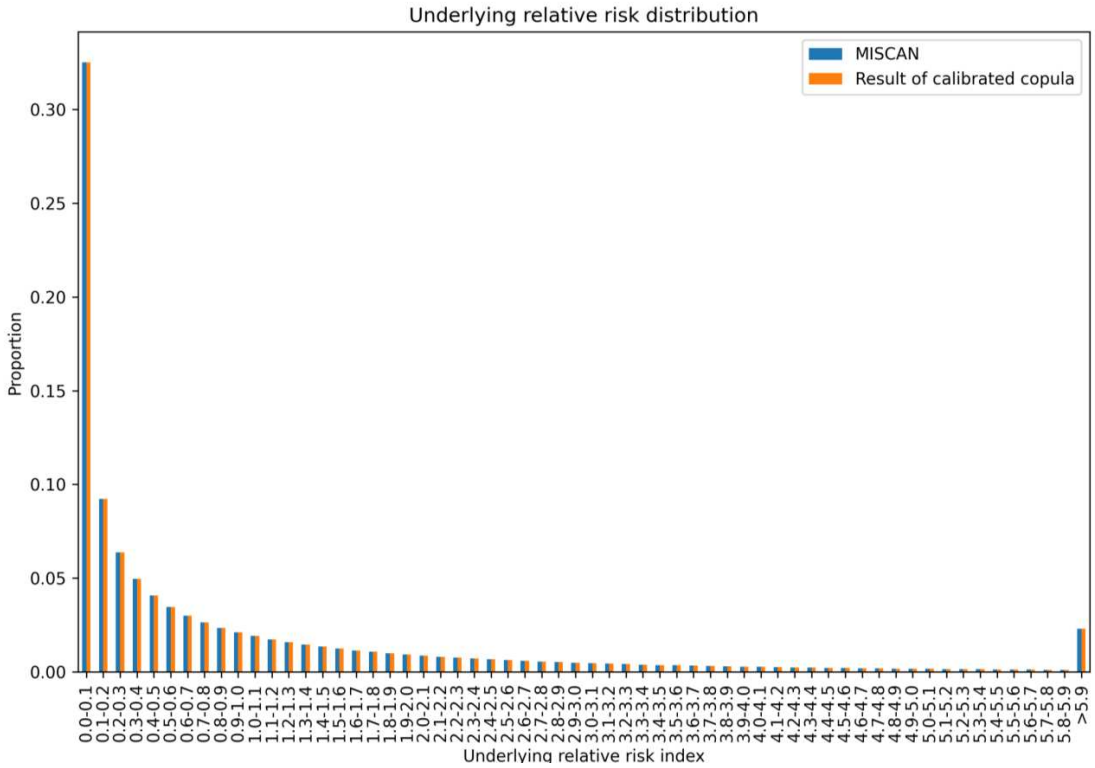

Figure S3.5 – Original distribution of underlying relative risk in MISCAN-Colon (blue), and the marginal distribution obtained with the copula (orange). The orange is the marginal distribution on top in Figure S3.2. The two are nearly equal which is in line with criterion 3.

3.3 – Assigning screening start ages

To determine what fraction of individuals started screening at each age, we took the following approach for both sexes. We used four QCancer-predicted risk thresholds to start screening (1%, 2%, 3% and 4%). First, we translated these risk thresholds to age- and sex-specific PRR thresholds by dividing them by the age- and sex-specific mean QCancer risk.

Then, we started with the joint distribution for age 25 to determine for each URR group what fraction of individuals exceeded the used PRR threshold for age 25. For these individuals, we set the screening start age at 25. Next, we used the joint distribution for age 30 to determine for each URR group what fraction of individuals exceeded the used PRR thresholds for age 30. We subtracted the fraction of individuals that had started screening at age 25, and set the screening start age at 30 for the remainder. We continued this process until we processed the joint distribution of age 70. The individuals that had not been assigned a screening start age by then are not screened during their lives because their QCancer-predicted risk did not exceed the risk threshold before the age of 70.

This approach assumes that, once individuals' predicted risk exceeded the risk threshold at a certain age, it will exceed the threshold during the remainder of their lives. As the predicted risk increases strongly with age, this assumes that individuals do not drastically change their lifestyle within 5 years. For example, a woman aged 60 that drinks more than 9 units of alcohol per day and is a heavy smoker has a 3.1% QCancer-predicted risk, and therefore starts screening at age 60 when using a risk threshold of 3%. If she maintains her lifestyle by age 65, she will have a risk of 4.2%, which

means her risk still exceeds the threshold. Also, if she becomes an ex-smoker and reduces her alcohol intake to 1-2 units per day, her risk by age 65 will be 3% which still satisfies our assumption. However, if she quits both smoking and drinking, her risk will drop to 2.8% at age 65, which is slightly below the threshold of 3%. Only such drastic change in lifestyle would violate our assumption.

3.4 – Sensitivity analysis with PRESENT study data

In our fifth sensitivity analysis, we used the PRESENT study data to determine the sex-specific QCancer risk distribution. As the number of participants in the PRESENT study is much smaller compared to SHS and most individuals in the PRESENT study were aged 50-53 (see Figure S3.7), it was not feasible to estimate QCancer risk distributions for each age and sex group. We therefore used all participants to generate the QCancer risk distributions for all age groups. For example, to determine the distribution for males aged 50, we set the age of all male PRESENT participants to 50 and then calculated their QCancer risk. We repeated the process for all other screening start ages and females. From there, we followed the same procedure as with the SHS data.

The underlying assumption of this is that the sex-specific prevalence of all risk factors except age does not change when individuals grow older, i.e. alcohol status, prevalence of prior cancer diagnoses and BMI distributions do not change over time. This is a relatively strong assumption because risk factors such as diabetes and past cancer diagnoses are more prevalent in older people. This approach is therefore likely to underestimate the prevalence of these risk factors, and to overestimate the age to start screening. For example, 60-year-old males without any risk factors would not be screened because their QCancer-predicted risk is 2.8%. However, by adding any risk factor, the predicted risk would exceed 3%. As such, this approach is likely to underestimate the number of 60-year-old males that are screen eligible under the Rapid Recommendation.

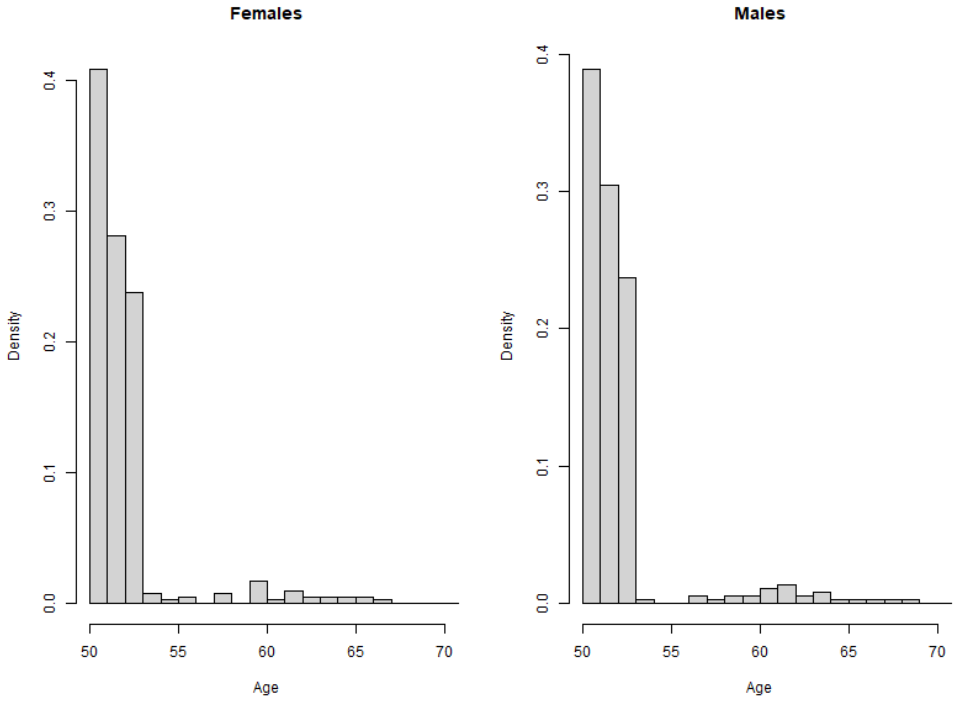

Figure S3.7 – Distribution of age of the participants in the PRESENT study.

3.5 – Sensitivity Analysis with hypothetical risk prediction model

In our seventh and eighth sensitivity analysis, we used a hypothetical, better risk prediction model instead of QCancer. For that, we used a copula that is a diagonal matrix (Figure S3.8). The risk prediction model therefore nearly perfectly predicts an individual's underlying risk of developing adenomas. However, due to the randomness in the simulations of MISCAN-Colon, a perfect prediction of underlying risk does not mean that we can perfectly predict whether someone will get CRC in the next 15 years. In our simulations we found that this hypothetical risk prediction tool would have an AUC of 0.84, independent of age and sex, whereas QCancer has an AUC of 0.66-0.70 in males and females aged 40-69.[19]

To determine at what age each PRR groups started screening, we derived the fraction of individuals that developed CRC within the next 15 year for each PRR group and start age. As soon as this fraction exceeded the risk threshold, the PRR group started screening. Consequently, the hypothetical risk prediction model was perfectly calibrated to the Swiss or Dutch population.

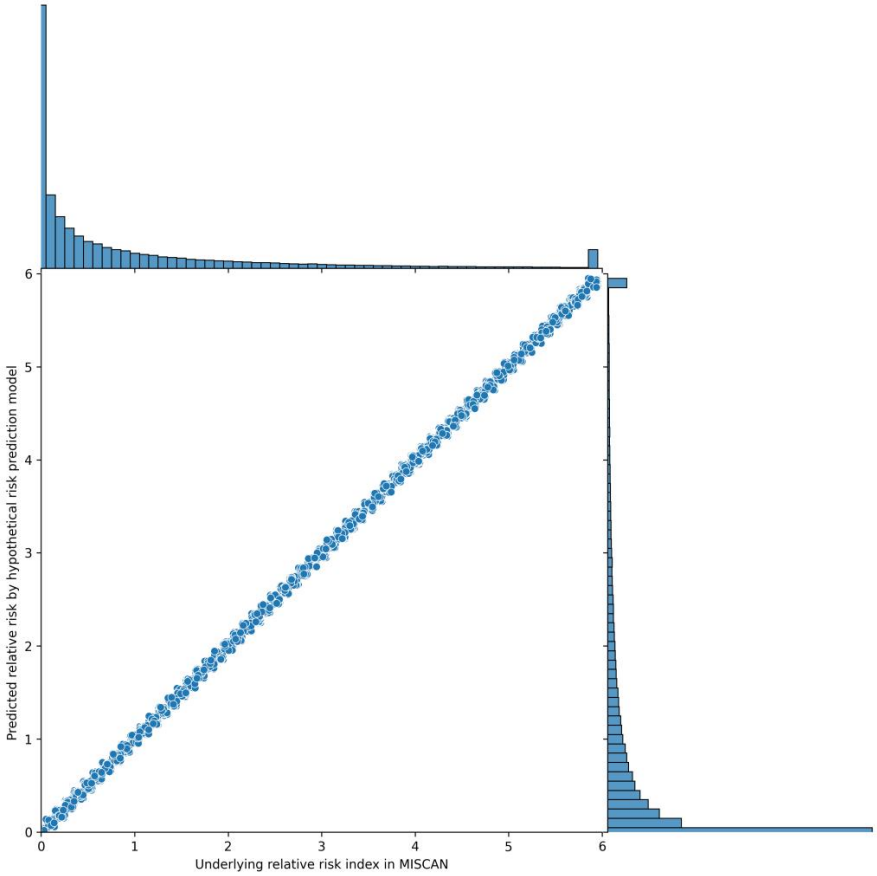

Figure S3.8 – Joint distribution of underlying and predicted relative risk for the hypothetical risk prediction tool with increased AUC. It applies to all age- and sex-groups as our risk-prediction tool is independent of age and sex. The top distribution is the marginal distribution of underlying risk in MISCAN. We assume that this hypothetical risk prediction model able to nearly perfectly estimates someone's underlying risk. Therefore, the distribution of predicted risk on the right and the underlying risk distribution in MISCAN are the same, and the copula is (almost) a diagonal line.

Appendix 4 – Test characteristics in MISCAN-Colon

Test characteristics			
	Colonoscopy	**FIT (males)**	**FIT (females)**
Specificity [a]	86%	92.11%	93.35%
Sensitivity [b]			
Adenoma 1-5 mm	75%	0.00% [c]	0.00% [c]
Adenoma 6-9 mm	85%	0.38%	1.09%
Adenoma 10+ mm	95%	23.2%	22.4%
Cancer	95%	68.5% / 91.3% [d]	60.9% / 88.2% [d]
Cutoff for positivity		15 µg/g	15 µg/g
Caecal intubation rate	94%		
Probability of fatal complication after colonoscopy with polypectomy	0.0000191% [e]		
Probability of hospitalization after colonoscopy with polypectomy	0.07% [f]		

a) The lack of specificity for colonoscopy reflects the detection of non-adenomatous lesions which are removed. This induces polypectomy and/or biopsy which might lead to complications after colonoscopy. The specificity of FIT represents the fraction of individuals that are referred for follow-up colonoscopy, independent of whether they have a lesion.
b) The values are per-lesion sensitivities. The sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[20]
c) MISCAN assumes that small adenomas cannot cause a positive stool test.
d) MISCAN assumes a higher sensitivity for lesions “short” before clinical diagnosis compared to “long” before diagnosis. The higher sensitivity applies to lesions that will show clinical symptoms in their current TNM stage. The lower applies to lesions that will first progress to a next TNM stage before showing clinical symptoms.
e) Risk of dying from a colonoscopy with polypectomy.[10]
f) Based on the most recent evaluation of the CRC screening program in the canton of Vaud, Switzerland.[3]

Appendix 5 – Results: distribution of screening start age

5.1 – Base Case and Sensitivity Analyses 1, 2 and 6

Table S5.1 – Proportion of females and males that would start screening at a certain age given the used risk threshold for CRC screening initiation. This distribution was used for the base case and sensitivity analyses 1, 2 and 6. It corresponds with Figure 2 in the main text. Screening start ages 25, 30 and 35 are omitted because nobody achieved these risk thresholds before age 40.

Start criterion	**Screening start age**							
	40	45	50	55	60	65	70	Never screened
Females								
Risk 1%	0%	9%	49%	41%	0%	0%	0%	0%
Risk 2%	0%	0%	1%	18%	81%	0%	0%	0%
Risk 3%	0%	0%	0%	1%	17%	56%	25%	0%
Risk 4%	0%	0%	0%	1%	2%	16%	41%	40%
Males								
Risk 1%	1%	7%	92%	0%	0%	0%	0%	0%
Risk 2%	0%	0%	6%	67%	26%	0%	0%	0%
Risk 3%	0%	0%	1%	9%	66%	24%	0%	0%
Risk 4%	0%	0%	0%	2%	21%	69%	7%	0%

5.2 – Sensitivity analysis 7 – Hypothetical, better risk prediction model in Switzerland

Table S5.2 – Proportion of females and males that would start screening at a certain age given the used risk threshold for CRC screening initiation, when using a hypothetical, better risk prediction tool in Switzerland (sensitivity analysis 7).

Screening start criterion	**Screening start age**										
	25	30	35	40	45	50	55	60	65	70	Never screened
Females											
Risk 1%	0%	0%	2%	6%	9%	11%	9%	6%	4%	5%	48%
Risk 2%	0%	0%	0%	2%	4%	7%	9%	7%	7%	3%	61%
Risk 3%	0%	0%	0%	0%	3%	5%	7%	6%	6%	4%	69%
Risk 4%	0%	0%	0%	0%	2%	2%	5%	6%	5%	4%	74%
Males											
Risk 1%	0%	0%	4%	8%	11%	11%	9%	9%	6%	0%	42%
Risk 2%	0%	0%	0%	3%	7%	11%	10%	8%	8%	0%	53%
Risk 3%	0%	0%	0%	2%	3%	8%	9%	9%	5%	6%	57%
Risk 4%	0%	0%	0%	0%	3%	6%	8%	9%	6%	5%	64%

5.3 – Sensitivity analysis 8 – Hypothetical, better risk prediction model in NL

Table S5.3 – Proportion of females and males that would start screening at a certain age given the used risk threshold for CRC screening initiation, when using a hypothetical, better risk prediction tool in The Netherlands (sensitivity analysis 8).

Screening start criterion	**Screening start age**										
	25	30	35	40	45	50	55	60	65	70	Never screened
Females											
Risk 1%	0%	2%	7%	11%	9%	10%	8%	5%	6%	0%	42%
Risk 2%	0%	0%	2%	6%	9%	9%	8%	9%	4%	0%	53%
Risk 3%	0%	0%	0%	4%	6%	9%	7%	8%	6%	3%	57%
Risk 4%	0%	0%	0%	2%	4%	8%	7%	7%	6%	3%	64%
Males											
Risk 1%	0%	3%	9%	11%	14%	11%	5%	6%	9%	0%	33%
Risk 2%	0%	0%	3%	8%	12%	11%	9%	4%	5%	6%	42%
Risk 3%	0%	0%	2%	3%	9%	10%	10%	9%	4%	0%	53%
Risk 4%	0%	0%	0%	3%	7%	9%	10%	7%	6%	0%	57%

Appendix 6 – Results: simulation outcomes

6.1 – Base case

Table S6.1 – Base case results. Outcomes are reported per 1000 CRC-free persons, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	13.5	7.8	104.0	9221	571	149	0.205	1176	73
Risk 2%	12.7	7.3	88.4	6260	445	87	0.170	858	61
Risk 3%	11.1	6.5	69.7	4130	322	61	0.137	638	50
Risk 4%	6.7	3.9	38.9	1813	152	35	0.076	465	39
Age 50	13.3	7.7	103.8	9655	589	158	0.207	1258	77
Age 55	13.6	7.9	99.7	8011	527	123	0.194	1012	67
Age 60	12.3	7.1	84.1	5830	425	78	0.162	823	60
Age 65	11.6	6.8	70.8	4322	341	61	0.142	637	50
Males									
Risk 1%	15.6	10.4	127	9034	619	170	0.196	868	59
Risk 2%	15.3	10.4	117.8	6810	516	108	0.171	658	50
Risk 3%	14.1	9.5	101.7	5083	420	67	0.144	537	44
Risk 4%	13.1	8.9	89.1	4015	350	50	0.126	450	39
Age 50	15.4	10.3	125.7	8852	613	163	0.193	858	59
Age 55	15.7	10.6	120.6	7235	541	118	0.177	682	51
Age 60	14.1	9.4	101.4	5211	431	66	0.145	555	46
Age 65	12.9	8.8	84.0	3765	336	44	0.121	426	38

6.2 – Sensitivity analysis 1 – Annual FIT screening

Table S6.2 – Results of sensitivity analysis 1 using annual FIT for screening. Outcomes are reported per 1000 CRC-free persons, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	17.5	9.6	126.4	14719	783	293	0.284	1533	81
Risk 2%	16.5	9.0	108.8	10126	655	144	0.235	1120	72
Risk 3%	14.7	8.1	86.4	6604	488	79	0.189	816	60
Risk 4%	9.2	5.1	50.2	3018	240	46	0.109	588	47
Age 50	17.7	9.7	128.3	15650	808	326	0.292	1618	84
Age 55	17.1	9.4	118.7	12548	734	219	0.261	1340	78
Age 60	16.3	8.9	104.8	9517	636	126	0.227	1066	71
Age 65	14.9	8.2	85.8	6686	506	69	0.190	816	62
Males									
Risk 1%	20.9	12.8	153.5	14231	823	357	0.279	1108	64
Risk 2%	20.0	12.3	139.6	10560	716	205	0.238	858	58
Risk 3%	18.8	11.6	123.5	7996	611	114	0.203	688	53
Risk 4%	17.4	10.8	107.6	6217	516	69	0.175	574	48
Age 50	20.8	12.8	152.5	13972	818	347	0.276	1091	64
Age 55	20.1	12.4	141.3	11104	738	226	0.243	897	60
Age 60	19.0	11.7	124.5	8306	633	118	0.207	709	54
Age 65	16.9	10.5	100.4	5723	495	51	0.166	543	47

6.3 – Sensitivity analysis 2 – 10-yearly colonoscopy screening

Table S6.3 – Results of sensitivity analysis 2 using 10-yearly colonoscopy for screening. Outcomes are reported per 1000 CRC-free persons, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of screening COLs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	25.3	11.5	134.9	2814	981	939	0.580	244	85
Risk 2%	23.0	10.5	116.5	1947	952	883	0.457	186	91
Risk 3%	22.1	10.3	100.4	1498	909	629	0.396	146	89
Risk 4%	13.9	6.5	59.6	676	530	183	0.216	104	82
Age 50	23.6	10.6	130.1	2778	986	949	0.556	263	93
Age 55	27.0	12.5	135.6	2648	971	918	0.577	213	78
Age 60	21.6	9.8	109.3	1779	947	874	0.422	182	97
Age 65	23.7	11.1	105.0	1664	914	804	0.430	150	82
Males									
Risk 1%	28.3	13.4	149.2	2705	978	915	0.524	202	73
Risk 2%	30.1	14.6	147.1	2247	942	838	0.490	154	65
Risk 3%	26.6	12.8	127.0	1695	899	760	0.399	132	70
Risk 4%	26.6	13.1	118.9	1484	859	648	0.374	113	66
Age 50	27.7	13.1	146.7	2642	977	911	0.513	202	75
Age 55	31.6	15.5	152.9	2438	951	854	0.523	158	61
Age 60	25.4	12.1	123.4	1656	908	778	0.383	137	75
Age 65	27.4	13.7	117.5	1476	849	667	0.378	108	62

6.4 – Sensitivity analysis 3 – Increased family history

Table S6.4 – Results of sensitivity analysis 3 with increased CRC family history prevalence. Outcomes are reported per 1000 CRC-free persons, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	13.5	7.8	103.0	8941	561	143	0.202	1141	72
Risk 2%	12.6	7.2	87.4	6160	440	85	0.168	850	61
Risk 3%	10.8	6.3	66.7	3889	306	59	0.132	616	49
Risk 4%	5.7	3.3	32.7	1449	123	29	0.063	440	37
Age 50	13.3	7.7	103.7	9655	589	158	0.207	1258	77
Age 55	13.6	7.9	99.6	8011	527	123	0.194	1012	67
Age 60	12.3	7.1	84.0	5830	425	78	0.162	823	60
Age 65	11.6	6.8	70.7	4322	341	61	0.142	637	50
Males									
Risk 1%	15.5	10.4	126.7	8988	617	168	0.195	865	59
Risk 2%	15.3	10.3	117.4	6746	513	106	0.17	652	50
Risk 3%	14.0	9.4	101.2	5039	417	66	0.144	533	44
Risk 4%	13.1	8.9	88.5	3973	347	49	0.126	446	39
Age 50	15.4	10.3	125.7	8852	613	163	0.193	858	59
Age 55	15.7	10.6	120.8	7235	541	118	0.177	682	51
Age 60	14.1	9.4	101.5	5211	431	66	0.145	555	46
Age 65	12.9	8.8	84.2	3765	336	44	0.121	426	38

6.5 – Sensitivity analysis 4 – Decreased family history

Table S6.5 – Results of sensitivity analysis 4 with decreased CRC family history prevalence. Outcomes are reported per 1000 CRC-free persons, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	13.6	7.9	105.1	9529	582	157	0.208	1211	74
Risk 2%	12.7	7.3	89.4	6364	449	89	0.172	866	61
Risk 3%	11.4	6.6	72.3	4359	337	63	0.141	657	51
Risk 4%	7.5	4.4	43.9	2126	177	40	0.086	485	40
Age 50	13.3	7.7	103.7	9655	589	158	0.207	1258	77
Age 55	13.6	7.9	99.7	8011	527	123	0.194	1012	67
Age 60	12.3	7.1	84	5830	425	78	0.162	823	60
Age 65	11.6	6.8	70.7	4322	341	61	0.142	637	50
Males									
Risk 1%	15.6	10.4	127.4	9092	621	172	0.196	871	60
Risk 2%	15.4	10.4	118.5	6908	521	110	0.173	665	50
Risk 3%	14.1	9.5	102.1	5114	422	68	0.145	538	44
Risk 4%	13.1	9.0	89.5	4043	352	50	0.127	452	39
Age 50	15.4	10.3	125.6	8852	613	163	0.193	858	59
Age 55	15.7	10.6	120.8	7235	541	118	0.177	682	51
Age 60	14.1	9.4	101.4	5211	431	66	0.145	555	46
Age 65	12.9	8.8	84.1	3765	336	44	0.121	426	38

6.6 – Sensitivity analysis 5 – PRESENT study data

Table S6.6 – Results of sensitivity analysis 5 using PRESENT study data to derive the QCancer risk distribution in the population. Outcomes are reported per 1000 CRC-free persons, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	13.6	7.9	103.6	9012	563	145	0.204	1144	71
Risk 2%	12.6	7.2	87.0	6117	438	84	0.167	846	61
Risk 3%	10.2	6.0	61.4	3501	280	55	0.123	588	47
Risk 4%	4.4	2.6	25.0	1134	97	23	0.050	439	38
Age 50	13.3	7.7	103.7	9655	589	158	0.207	1258	77
Age 55	13.6	7.9	99.6	8011	527	123	0.194	1012	67
Age 60	12.3	7.1	84.0	5830	425	78	0.162	823	60
Age 65	11.6	6.8	70.7	4322	341	61	0.142	637	50
Males									
Risk 1%	15.6	10.5	128.5	9263	626	177	0.199	885	60
Risk 2%	15.3	10.3	118.1	6862	518	109	0.172	664	50
Risk 3%	14.1	9.5	102.4	5159	424	69	0.146	543	45
Risk 4%	13.3	9.1	90.7	4171	362	51	0.129	460	40
Age 50	15.4	10.3	125.7	8852	613	163	0.193	858	59
Age 55	15.7	10.6	120.7	7235	541	118	0.177	682	51
Age 60	14.1	9.4	101.4	5211	431	66	0.145	555	46
Age 65	12.9	8.8	84.1	3765	336	44	0.121	426	38

6.7 – Sensitivity analysis 6 – Dutch natural history of CRC

Table S6.7 – Results of sensitivity analysis 6 using the Dutch version of MISCAN-Colon. Outcomes are reported per 1000 CRC-free persons, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	26.3	16.6	224.8	9075	602	198	0.305	547	36
Risk 2%	25.0	15.5	187.9	6135	480	136	0.257	396	31
Risk 3%	22.4	13.9	146.4	4047	357	105	0.210	292	26
Risk 4%	13.6	8.4	81.5	1773	174	62	0.118	210	21
Age 50	25.9	16.3	225.4	9513	620	205	0.307	584	38
Age 55	26.5	16.6	212.1	7863	561	173	0.289	472	34
Age 60	24.5	15.1	178.3	5716	461	127	0.246	379	31
Age 65	23.5	14.6	148.0	4240	377	106	0.217	291	26
Males									
Risk 1%	29.5	19.9	261.3	9298	658	211	0.273	467	33
Risk 2%	29.3	19.6	237.9	7067	562	147	0.243	360	29
Risk 3%	27.2	18.0	202.3	5313	467	103	0.208	295	26
Risk 4%	25.4	16.9	174.2	4231	396	83	0.183	251	23
Age 50	29.3	19.8	258.1	9114	652	205	0.270	461	33
Age 55	29.9	20.1	243.9	7506	587	159	0.250	374	29
Age 60	27.3	17.9	201.8	5443	478	102	0.209	304	27
Age 65	25.0	16.6	162.4	3988	383	77	0.176	240	23

6.8 – Sensitivity analysis 7 – Hypothetical, better risk prediction model in Switzerland

Table S6.8 – Results of sensitivity analysis 7 using the hypothetical, better risk prediction tool to replace QCancer in Switzerland. Outcomes are reported per 1000 CRC-free persons compared, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	12.9	7.5	102.3	4458	287	101	0.168	595	38
Risk 2%	11.8	6.8	90.6	2823	207	75	0.141	412	30
Risk 3%	10.8	6.3	80.4	1953	158	61	0.121	312	25
Risk 4%	9.9	5.7	71.9	1453	126	53	0.105	254	22
Age 50	13.3	7.7	103.7	9655	589	158	0.207	1258	77
Age 55	13.6	7.9	99.7	8011	527	123	0.194	1012	67
Age 60	12.3	7.1	84.0	5830	425	78	0.162	823	60
Age 65	11.6	6.8	70.7	4322	341	61	0.142	637	50
Males									
Risk 1%	15.3	10.4	128.5	5024	347	113	0.164	485	33
Risk 2%	14.4	9.7	118.2	3473	263	82	0.142	357	27
Risk 3%	13.5	9.2	109.5	2651	214	66	0.127	289	23
Risk 4%	12.7	8.7	101.3	2065	178	56	0.114	238	21
Age 50	15.4	10.3	125.7	8852	613	163	0.193	858	59
Age 55	15.7	10.6	120.8	7235	541	118	0.177	682	51
Age 60	14.1	9.4	101.4	5211	431	66	0.145	555	46
Age 65	12.9	8.8	84.1	3765	336	44	0.121	426	38

6.9 – Sensitivity analysis 8 – Hypothetical, better risk prediction model in The Netherlands

Table S6.9 – Results of sensitivity analysis 8 using the hypothetical, better risk prediction tool to replace QCancer in The Netherlands in combination with the Dutch version of MISCAN-Colon. Outcomes are reported per 1000 CRC-free persons compared, except NNScreen (Number of tests per CRC death prevented) and NNScope (Number of individuals with at least one colonoscopy per death prevented). All outcomes are reported compared to a scenario without screening.

	Benefits			**Burdens**			**Harms**	**Ratios**	
Start criterion	CRC cases prevented by screening	CRC deaths prevented by screening	Lifeyears gained by screening	Number of FITs	Number of individuals with >=1 COL	Number of individuals with >=2 COLs	Hospitalizations due to screening	NNScreen	NNScope
Females									
Risk 1%	25.8	16.5	237.5	5909	379	170	0.289	358	23
Risk 2%	24.6	15.7	220.7	4060	298	138	0.257	258	19
Risk 3%	23.6	15.0	205.4	3105	254	123	0.235	208	17
Risk 4%	22.5	14.1	191.0	2430	216	110	0.213	172	15
Age 50	25.9	16.3	225.4	9513	620	205	0.307	584	38
Age 55	26.5	16.6	212.0	7863	561	173	0.289	472	34
Age 60	24.5	15.1	178.3	5716	461	127	0.246	379	31
Age 65	23.5	14.6	147.9	4240	377	106	0.217	291	26
Males									
Risk 1%	29.6	20.4	277.5	6669	447	181	0.260	328	22
Risk 2%	28.6	19.6	262.6	4858	357	142	0.235	248	18
Risk 3%	27.4	18.8	248.9	3810	300	121	0.215	203	16
Risk 4%	26.5	18.1	236.6	3183	267	108	0.201	176	15
Age 50	29.3	19.8	258.1	9114	652	205	0.270	461	33
Age 55	29.9	20.1	244.1	7506	587	159	0.250	374	29
Age 60	27.3	17.9	201.9	5443	478	102	0.209	304	27
Age 65	25.0	16.6	162.6	3988	383	77	0.176	240	23

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References

1. Sandhu MS, Luben R, Khaw KT. Prevalence and family history of colorectal cancer: implications for screening. Journal of Medical Screening. 2001;8(2):69-72.
2. Prévalence du cancer: Foundation National Institute for Cancer Epidemiology and Registration; [updated 25th January 2022. Available from: https://www.onec.ch/fr/statistiques-atlas/les-statistiques-national-sur-la-prevalence-du-cancer/.
3. Brändle K, Arveux P, Germann S, Bochud M, Bulliard J-L. Première évaluation du programme vaudois de dépistage du cancer colorectal, 2015-2020. Raisons de Santé. 2022(335):75.
4. Enquête suisse sur la santé: Office fédéral de la statistique; [Available from: https://www.bfs.admin.ch/bfs/fr/home/statistiques/sante/enquetes/sgb.html.
5. QCancer®(15yr,colorectal) risk calculator [updated 15th March 2019. Available from: https://qcancer.org/15yr/colorectal/index.php.
6. Cancer today: population fact sheets: International Agency for Research on Cancer, WHO; [Available from: https://gco.iarc.fr/today/fact-sheets-populations.
7. Van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations in R. Journal of statistical software. 2011;45:1-67.
8. Plys E, Bulliard J-L, Chaouch A, Durand M-A, Van Duuren LA, Brändle K, et al. Colorectal Cancer Screening Decision Based on Predicted Risk: Protocol for a Pilot Randomized Controlled Trial. JMIR research protocols. 2023;12(1):e46865.
9. Loeve F, Boer R, Van Oortmarssen GJ, Van Ballegooijen M, Habbema JDF. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Computers and Biomedical Research. 1999;32(1):13-33.
10. Van Hees F, Zauber AG, Van Veldhuizen H, Heijnen M-LA, Penning C, De Koning HJ, et al. The value of models in informing resource allocation in colorectal cancer screening: the case of the Netherlands. Gut. 2015;64(12):1985-97.
11. Gini A, Buskermolen M, Senore C, Anttila A, Novak Mlakar D, Veerus P, et al. Development and validation of three regional microsimulation models for predicting colorectal cancer screening benefits in Europe. MDM Policy & Practice. 2021;6(1):2381468320984974.
12. Fortin F-A, De Rainville F-M, Gardner M-AG, Parizeau M, Gagné C. DEAP: Evolutionary algorithms made easy. The Journal of Machine Learning Research. 2012;13(1):2171-5.
13. Faivre J, Bossard N, Jooste V. Trends in net survival from colon cancer in six European Latin countries. European Journal of Cancer Prevention. 2017;26:40-7.
14. Lepage C, Bossard N, Dejardin O, Carmona-Garcia MC, Manfredi S, Faivre J. Trends in net survival from rectal cancer in six European Latin countries. European Journal of Cancer Prevention. 2017;26:48-55.
15. Lutz JM, Pury P, Fioretta G, Raymond L. The impact of coding process on observed cancer mortality trends in Switzerland. European Journal of Cancer Prevention. 2004:77-81.
16. Naber SK, Kundu S, Kuntz KM, Dotson WD, Williams MS, Zauber AG, et al. Cost-effectiveness of risk-stratified colorectal cancer screening based on polygenic risk: current status and future potential. JNCI cancer spectrum. 2020;4(1):pkz086.
17. Van den Puttelaar R, Meester RGS, Peterse EFP, Zauber AG, Zheng J, Hayes RB, et al. Risk-stratified screening for colorectal cancer using genetic and environmental risk factors: A cost-effectiveness analysis based on real-world data. Clinical Gastroenterology and Hepatology. 2023.
18. Mai J-F, Scherer M. Simulating copulas: stochastic models, sampling algorithms, and applications: # N/A; 2017.
19. Usher-Smith JA, Harshfield A, Saunders CL, Sharp SJ, Emery J, Walter FM, et al. External validation of risk prediction models for incident colorectal cancer using UK Biobank. British journal of cancer. 2018;118(5):750-9.
20. Van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, Van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Official journal of the American College of Gastroenterology| ACG. 2006;101(2):343-50.